Treatment of heart failure and patient outcomes in real life

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General discussion

GENERAL DISCUSSION

This thesis assesses the impact of heart failure (HF) treatment on patient outcomes in real-life heart failure setting. We concentrated on the effectiveness of pharmacological treatment in HF, with special focus on the effect of beta blocker therapy. Two main patient-related outcomes are assessed in relation with pharmacological treatment, quality of life and survival. In this chapter, we present the main findings of the studies included in this thesis, and we discuss the implications of the findings for clinical practice and future research.

SUMMARY OF THE MAIN FINDINGS

First aim: The impact of pharmacological treatment on quality of life

Improving quality of life (QoL) is a main aim of current treatment in HF.[1] To assess the evidence-based background on this health-related outcome, in **Chapter 2,** we performed a meta-analysis of RCTs to quantify the impact of beta blocker therapy on QoL in patients with HF receiving optimal standard medication. At present, there are conflicting hypotheses regarding the impact of beta blocker therapy on QoL. Primarily, an improvement in QoL is expected, due to beneficial effects on cardiac function and hospitalisations.[2] On the other hand, QoL might be adversely affected due to the side effects of beta blocker medication, especially during the initiation of therapy.[3] A total of nine RCTs involving 1954 patients were included into analysis. QoL was assessed through a disease specific instrument, the Minnesota Living with Heart Failure questionnaire (MLHF)[4] or the Quality of Life with Heart Failure questionnaire (QLHF).[5] We found that beta blocker therapy, on top of standard medication, does not affect QoL (neither improvement nor impairment). However, there is a trend towards better QoL in HF patients additionally treated with beta blockers. This result was independent on the type of beta blocker or severity of disese. The highest impact on QoL appears in short follow-up (three months therapy). However, this effect may be attributed to multiplicity, i.e. it is one of several groups considered and by chance it shows a significant result. This neutral effect of beta blockers may be due to several reasons, including a balance between beneficial and side effects, low sensitivity of QoL questionnaire (MLHF), or simply no effect of beta blocker therapy on QoL when added on top of standard medication.

In **Chapter 3,** we explored whether evidence-based drug therapy is associated with better quality of life (QoL) in daily practice HF patients. QoL was assessed with the RAND 36-item health survey questionnaire.[6] Medication was classified as either evidence-based treatment or under-treatment, according to the 2001 European guidelines on HF treatment.[7] Only 57% of the patients were prescribed evidence-based treatment regimens, while 43% received treatment patterns including less than recommended drugs. Under-treatment was more frequent as severity of disease increased, ranging from 33% in NYHA I to almost 70% in NYHA III and IV. However, we found that conventional step-up medication approach in HF is not associated with better QoL. Similar to our meta-analysis of RCTs, this study shows that current HF medication may improve survival but does not seem beneficial in relation to QoL.

Current treatment goals in HF aim to improve both survival and QoL of patients. In **Chapter 4,** we reviewed RCTs that assessed the impact of life prolonging therapies on QoL, and we discussed some methodological limitations of QoL assessment in HF. Studies that assessed QoL with a disease specific questionnaire were included. We found that at present there is a paradox in HF treatment. Life prolonging therapies, such as Angiotensin-converting-enzime-inhibitors (ACEI), and Angiotensin receptor blockers improve modestly or only delay the progressive worsening of QoL in HF. Treatment with beta blockers does not affect QoL in any way. However, this neutral effect of beta blockers may also be due to some methodological limitations, such as the small number of patients included in beta blocker trials or the short duration of follow-up. Disease specific questionnaires may also have some limitations, e.g. are not sensitive enough to detect small changes in QoL. On the other hand, therapies that significantly improve QoL in HF (e.g. inotropic agents) do not seem beneficial in relation to survival. We conclude that assessment of QoL in HF remains an open field, in which new therapies but also clarification of methodology is required. In the mean time, the use of life prolonging therapies appears as a safe measure to modestly improve or maintain QoL.

Second aim: The impact of pharmacological treatment on survival

In **Chapter 5**, we aimed to assess the contribution of observational studies to actual knowledge regarding drug effectiveness in patients with HF. For this purpose, we reviewed observational studies of drug effectiveness published between 1990-2005. A total of 23 observational studies were included. We found that observational studies in HF validate

the effectiveness of ACEI and beta blockers in patient populations underrepresented or excluded from RCTs, such as elderly patients with a broad range of EF, elderly with depressed EF, and patients with renal insufficiency. Low-dose ACEI and beta blocker may have beneficial effects. Target doses of ACEI seem superior to low-doses, but there is no clear dose-response relationship. Effectiveness of ACEI and beta blockers in HF with preserved LVEF is not clear from actual published studies, although last evidence suggest a potential benefit of ACEI. We conclude that observational studies of drug effectiveness provide necessary additional information for clinical practice.

Patients in daily practice are older, have more comorbidities, and high prevalence of preserved LVEF, compared to patients enrolled in RCTs.[8,9] In addition, beta blockers are frequently prescribed at doses lower than those investigated in clinical trials.[10] In **Chapter 6,** we assessed *first,* whether prescription of a β-blocker at discharge is associated with better survival in a daily practice cohort of patients with HF, and *second,* whether this association is modified by the age of the patient. Patients with advanced HF (NYHA III and IV) were included into the study, irrespective of LVEF (45% had EF>40%). In total, 625 patients were included, and the cohort was followed-up for an average of 22 months. We found that prescription of a beta blocker was associated with a significant mortality reduction (45% relative risk reduction). The numbers needed to treat (NNT) to avoid one death was 20 patients for six months, and 10 patients for two years. The relative risk reduction was similar with prescription of low- or high doses of beta blockers. However, the beneficial effects of beta blockers appeared to be higher in younger patients, particularly in those younger than 80 years.

Given the high percentage of patients with preserved LVEF, and the lack of evidence-based therapy for its management,[11] in **Chapter 7** we assessed specifically the association between beta blocker prescription at discharge and survival in a daily practice cohort of patients with HF and preserved LVEF. We prospectively studied a cohort of 443 patients with advanced HF and preserved LVEF (LVEF≥40). Mean duration of follow-up was 25 months. We found that prescription of a beta blocker was associated with a significant mortality reduction (43% relative risk reduction). The relative risk reduction appeared to be dose related, with high-dose rather than low-dose therapy being associated with a lower risk of death. This evidence on the beneficial effects of beta blocker use needs to be further confirmed in prospective, randomised clinical trials.

In elderly patients with HF, prescription of a beta blocker raise two major concerns, tolerability and efficacy. In RCTs beta blockers are carefully up-titrated until the target dose or the last tolerated is achieved. This may be different from clinical practice, where the reasons for prescription of subtarget doses may be more difficult to evaluate. In **Chapter 8** we performed a post-hoc analysis in the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) trial[12] to assess tolerability and dose-related effects of the beta blocker nebivolol in elderly patients with HF. We analysed the data by classifying the patients assigned to nebivolol into four groups, according to the dose achieved at the end of titration phase: 0 mg, low dose (1.25 or 2.5 mg), medium dose (5 mg), and target dose (10 mg). Overall, 67% patients tolerated the target dose, and only 7% were unable to tolerate any dose. After adjustment, all cause mortality or cardiovascular (CV) hospitalisation was significantly reduced in the target dose nebivolol group compared to placebo (25% relative risk reduction). The medium dose nebivolol group had rather a similar benefit as high dose (27% relative risk reduction), although of borderline statistical significance, while the low dose group achieved a non-significant benefit (12% relative risk reduction). Patients unable to tolerate any dose of nebivolol had a two-fold higher risk of death or CV hospitalisation. We concluded that the beta blocker nebivolol is well tolerated in elderly HF population. Higher doses (i.e. medium to target) appear superior to low doses. Patients who cannot tolerate any dose have the worst outcome.

What our studies add to previous knowledge?

In conclusion, our studies add *four main findings* to previous knowledge:

First, beta blocker therapy and evidence-based therapy that improves survival in HF does not seem largely beneficial in relation to QoL. Nevertheless, the use of life prolonging therapies appears as a safe measure to maintain or modestly improve QoL.

Second, treatment with beta blockers improves survival in daily practice patients with advanced HF and a broad range of LVEF. However, the effect of beta blocker therapy on survival seems to be higher in younger patients, particularly those younger than 80 years.

Third, treatment with beta blockers may be beneficial in HF with preserved LVEF.

Fourth, dose of nebivolol might be an important outcome modifier. Higher doses (medium to target) seem superior to low doses. Patients unable to tolerate any dose have the worst outcome.

IMPLICATIONS FOR CLINICAL PRACTICE

Should all patients with heart failure receive a beta blocker?

It is hard to give a straightforward answer to this question. In average daily practice populations our data show that prescription of a beta blocker is beneficial in relation to survival. Our data provide more certainty for the clinician that medication proved to be efficient in randomised trials is also effective in real-life heart failure setting. Patients who do not have absolute contraindications to beta blocker therapy (e.g advanced heart block, asthma or reactive airways disease that requires bronchodilator therapy, heart rate < 50 bpm, and sytolic blood pressure < 85 mm Hg)[13] should be therefore considered for beta blocker initiation. However, we also show that the effect of beta blocker medication on survival might be lower in the very elderly. Previous studies have also suggested that the effect of beta blocker therapy may be lower in patients with atrial fibrillation.[14] Further, beta blockers is recommended to be used with caution in other co-morbidities, such as COPD and depression.[13] On the other hand, beta blocker therapy does not seem largely beneficial in relation to QoL. The clinician has to balance the findings at population level with the individual patient. In this context, we recommend prescription of a beta blocker in conjuction with a complete clinical assessment, which includes not only pathophysiological understanding of the disease, age, concomitant comorbidities, tolerability, but also patient preferences.[15]

Given the current evidence, there is no doubt that beta blocker therapy and life prolonging therapies in general remain the therapy of election for most patients with HF. However, these findings raise ethical concerns over the use of symptom relief (e.g. diuretics, digitalis) or QoL improvement therapies (e.g. inotropic agents) instead of life prolonging therapies in certain subsets of heart failure populations, such as very elderly, patients with refractory symptoms for whom transplantation or device implementation is not an option, or individuals with terminal malignancy.

At present, beta blockers are largely underprescribed in daily practice.[16] Various reasons may explain this low prescription, but fear of side effects is common. This is despite a large body of evidence that show that beta blockers are rather well tolerated, even in elderly populations.[10,17] While in medicine the first principle remains "prima non nocere" - first do not harm, it may be overlooked that HF patients are at high risk for major cardiovascular events. Therefore, the benefit of treatment may overcome the side effects. As such, patients may be deprived of one of the most effective therapies at present.

What dose of beta blocker should be prescribed?

Previous studies have shown that patients with HF and depressed LVEF have a similar benefit on survival with dispensing of low- or high dose beta blocker therapy (low- and high dose therapy being defined as less or more than 50% of target dose achieved in RCTs).[18] Similarly, in HF patients with a broad range of LVEF a similar effect of low- and high dose therapy was observed.[19]

However, in patients with preserved LVEF we observed a higher benefit of high-dose therapy, although in fact high dose group comprised mainly patients on medium dose beta blocker.[20] Therefore, these data rather suggest that patients who achieve at least medium doses do better than those on lower doses. Subgroup analysis in the SENIORS trial also show that higher doses (i.e. medium to target) seem superior to low doses.
Our data suggest therefore that when target doses of beta blockers cannot be achieved, efforts should be made to reach at least medium doses.

IMPLICATIONS FOR FUTURE RESEARCH

Methodological issues

Observational studies of drug effectiveness are essential to evaluate the usefulness of treatments and interventions in real-life heart failure setting.[21] However, at present they are still perceived as a second-class analysis due to methodological limitations inherent to any observational design. Patients in daily practice are very complex, and providers allocate treatment based on many criteria. Multivariate adjustment and other statistical methods are used to deal with patient heterogeneity, but residual confounding will always remain an issue.[22,23] However, two landmark systematic reviews and meta-analysis found a similar effect of medication in well-designed observational studies and RCTs, and they challenged the current hierarchy of study designs in clinical research.[24,25] This information is important, but from the methodological point of view one would expect in most cases different results.[26] More empirical evidence is therefore needed to understand what exactly each study design tells us and what each study may add to the other. Such analysis would be very important to understand the merits of observational design, and to choose the appropriate method in various clinical circumstances.

Heart failure with depressed versus preserved LVEF

One important issue to explore in future research is the role of pharmacological treatment in HF with preserved LVEF. More observational studies (along with RCTs) are needed

to provide accurate information regarding drug effectiveness in this specific group. However, to provide reliable information on drug effectiveness, an accurate diagnostic tool for HF with preserved LVEF has to be identified. The actual definition based on symptoms of HF and preserved LVEF pose the risk of misdiagnosis, and the assessment of diastolic dyfunction as a cause of symptoms remains a difficult and controversial test.

QoL assessment

Medication that improves survival in HF does not seem largely beneficial in relation to QoL. To further explore the impact of beta blocker therapy on QoL, a meta-analysis of RCTs and observational studies should be conducted. Such analysis would have more power to detect a potential beneficial effect of beta blockers on QoL, not only by increasing the sample size, but also through a longer patient follow-up. In addition, the validity of QoL disease specific questionnaires have to be further explored.

Future therapies in HF

In this thesis we limited our research to the most important drug therapies in HF. Despite clear benefit on survival with current drug therapies, mortality in HF remains very high. Aditionally, the benefit of current therapies on patients' QoL is limited. Other options, such as stem cell therapy, may achieve a higher benefit on both survival and QoL of patients with HF in the near future.

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